# Advising Patients with Hereditary Eye Disease

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# ADVISING PATIENTS WITH HEREDITARY EYE DISEASE

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Hereditary features have been reported in connection with every part of the eye. Even such conditions as dacryocystitis and recurrent corneal erosion are familial in isolated instances. Although most of these familial characteristics are only of academic interest, there are several serious conditions which are frequently familial, and it is particularly important for them to be understood. Merely to recognize a hereditary disease is certainly not enough. One must diagnose the type of inheritance and make predictions for the patient's offspring as well as other members of his family.

Abnormal genes affecting the eye make their presence known by producing either dominant, recessive, or sex-linked recessive traits. Often the word "autosomal" is used to characterize those traits which appear freely in both men and women alike, without being affected by the sex of the individual.

Every abnormality must begin somewhere, and patients may appear with a disease which they are going to transmit to many generations in the future, although their family history is completely negative. These patients are living mutants, and the defective gene first appears in them.[†]

## Dominant traits

Dominant traits are always obvious. That is, if a person carries the gene for a simple dominant feature, then he must show the feature be it glaucoma, cataract or aniridia. If a particular disease is inherited as a dominant trait, there will be many affected individuals in the family tree. Approximately 50 percent of the members in each generation should show the abnormality.

When confronted with a patient whose eye malady is inherited as a dominant trait, one can make predictions with reasonable accuracy for future offspring (see tables 1 and 2):

1. If the patient is young, his parents may wish to know the likelihood of this disease appearing in their future children. They can be told with reasonable accuracy that the next child will have a 50-percent chance of developing the disease.
2. As for the patient himself, assuming that he will marry a normal person, 50 percent of his future children will be affected.
3. The normal members of this family, such as brothers, sisters, aunts, and uncles, cannot be carrying the dominant gene and need not fear the possibility of having affected children. Only in irregular circumstances can anyone transmit a dominant gene

TABLE 1

How to determine the mode of inheritance

Dominant
1. One of the parents is affected
2. Fifty percent of the members are affected
3. Normal members have all normal children

Recessive
1. Neither parent is affected
2. The parents are usually related (consanguineous union)
3. Twenty-five percent of the siblings are affected
4. Affected members have normal children*
5. Normal members have normal children*

Sex-linked recessive
1. Affects only men
2. Transmitted via the normal women
3. Affected men have normal children*
4. Normal women have 25 percent of their children affected (i.e., 50 percent of the males, no females)

* Normal here means the phenotype. The individual may still be a carrier but will not have the disease.

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[†] It is thought that all hereditary traits originate as mutations, which are the result of alterations within the complex amino-acid molecules composing the genes in the reproductive cells. These alterations may take place in the normal parents as a result of trauma, radiation, biochemical effects, or reduction division.

TABLE 2

What are the chances my next child will develop the disease?

| Type of Heredity | Person Asking Question | | | |
|---|---|---|---|---|
| | Parents of the Patient | The Patient | Normal Aunts & Uncles | Affected Aunts & Uncles |
| Dominant | 50% | 50% | 0 | 50% |
| Recessive | 25% | 0 | 0 | 0 |
| Sex-linked recessive | (50% of sons)<br>(none of daughters)<br>25% | 0 | Women 25% or less<br>Men 0 | Affected uncles may transmit but will have normal children. |

without himself giving evidence that this particular gene lies in his own germ plasm.

Sometimes there will occur the confusing feature of glaucoma being transmitted by a person with seemingly normal eyes. This is an instance of what is called "irregular dominance." It may represent an effect of environment upon heredity, that is, perhaps the patient has lived a protected life free from emotional trauma, and this has allowed him the privilege of normal eyes although he does have a tendency to glaucoma. Certainly one cannot accept the report from relatives that any member has normal eyes if the rules of heredity direct that he should have the disease. Even after examination with negative provocative tests, this individual may later acquire true glaucoma. One practical value in recognizing hereditary glaucoma lies in the fact that seemingly normal members of such a family must be followed very carefully.

Figure 1 characterizes the typical family tree for the dominant trait glaucoma. It is evident that affected members transmit the disease to approximately half of their offspring and unaffected members never transmit the trait. The first affected member at the head of the family tree, of course, acquired the defect from his normal parents because of a mutation.

Retinoblastoma is a dominant trait which merits some discussion. Usually children with retinoblastoma are brought to the ophthalmologist by parents who have perfectly normal eyes.

First consider the parents. Could either of them possess the gene for retinoblastoma? Since the gene is a dominant one and neither parent has the disease, it can be assumed

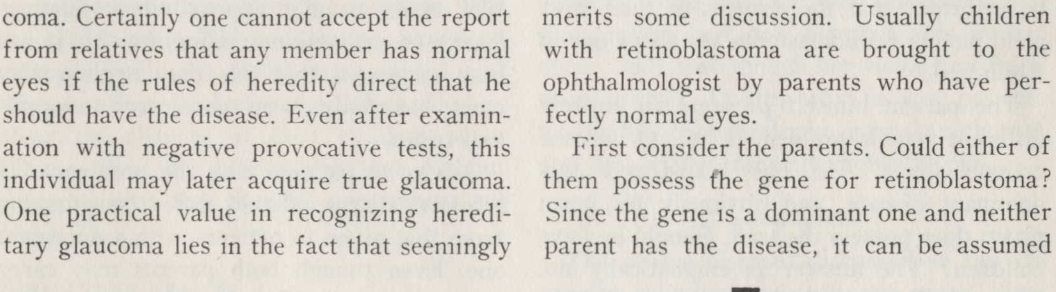

Fig. 1 (Manchester). Dominant glaucoma. All are patients of Dr. F. P. Calhoun. Squares indicate men, circles indicate women. Affected individuals are in black.

that they do not carry the gene and their affected child must represent an example of mutation. Their other children should be normal, since neither of these parents is a carrier of retinoblastoma.

How often do these parents ask the ophthalmologist: "May we have another child? And if we do, how likely are we to relive the same tragedy again with a second child similarly marked by retinoblastoma?"

Theoretically, they have no chance of bringing forth another child with retinoblastoma because they do not possess the abnormal gene. This statement should be made with a slight reservation, as there may be some unknown environmental or cellular factor which produced the one deformed child and by the same physical or chemical action it might cause a second mutation. Actually in the literature, 595 sporadic cases of retinoblastoma have been studied.[1] Of these, only seven siblings developed retinoblastoma. Consequently, the parents should be informed that the chances of their next child having retinoblastoma are about one in a hundred.

The patient himself presents an entirely different genetic problem if he survives the retinoblastoma. He has manifested this dominant disease, and obviously his germ plasm does possess the trait. Should he have children? The answer is emphatically no. Theoretically each of his offspring will have a 50-50 chance of getting retinoblastoma. Actually, of those cases which are on record, the incidence is even higher than has been calculated.

The responsibility of the ophthalmologist goes beyond diagnosing and treating the retinoblastoma. Parents of the patient should be advised to have more children, as this may be a great consolation to them, since their next child should be normal. On the other hand, anyone who has survived a retinoblastoma must be forbidden to have offspring because the odds are so great against their ever escaping the disease.[2,3]

Cataracts of many types have been known to show a dominant hereditary tendency. However, most cases of cataract are merely sporadic and are not in any way hereditary. On the contrary, other dominant traits such as aniridia, blue sclerotics, phakomatoses, arachnodactyly, and retinoblastoma are practically always hereditary and, therefore their genetic features must be given careful consideration routinely.[4-12]

## Recessive traits

Recessive traits are the hidden ones. It has been calculated that each of us possesses the gene for at least one important physical defect which we do not show because it is recessive. When two people marry both of whom happen to transmit the same hidden trait, the offspring may then actually show the defect. Thus a "double dose" is necessary for recessive genes to produce any effect on a child. Since members of the same family are more likely to have the same hidden genes, recessive traits usually appear when relatives marry (consanguinous union, fig. 2). It has been suggested that this may explain why incest has always been taboo, even in primitive tribes.

Advice to patients with the problem of a recessive disease should differ considerably from that given to patients with a dominant one. Even though both parents may carry a recessive trait, the chances are only 1:4 that their next child will get a gene from

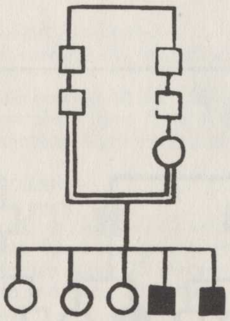

Fig. 2 (Manchester). Recessive Laurence-Moon-Biedl syndrome. Patients of Dr. F. P. Calhoun. Double lines indicate consanguinity.

each parent and manifest the disease. As for the patient himself, if his mate is normal, he will not transmit the abnormality to any of his children. All of them must be normal. They may be carriers, of course, but they will never develop the disease because they receive only one gene from their affected parent and one from his normal mate. A defective gene must come from each parent before the disease itself will be apparent.

Pure albinism is an example of a recessive trait. If normal parents appear with an albino child, inquiry should be made regarding consanguinity because this is such a frequent explanation for the appearance of recessive traits. These parents might want to know the chances that their next child will be likewise affected with albinism. The answer is 1:4. A second question which may be posed is the likelihood of this first albino child having affected children when he marries. It is interesting that all of his children must be normal, unless, by chance, he marries another albino or someone with the hidden trait. This, of course, would be extremely unlikely. If the aunts, uncles, and other unaffected members of this family ask about the chances of their children being albinos, they can be assured that without consanguinity the chances are almost nil (table 2).

### SEX-LINKED TRAITS

Sex-linked traits are peculiar in one respect, from the standpoint of ophthalmology. They are transmitted by both sexes but they affect only the men.* In other words, though men are the only ones who suffer from these inherited traits, actually the women with normal eyes bear much of the responsibility of carrying them on to the next generation.

It is not difficult to give sound advice regarding sex-linked traits. The parents should be informed that half their sons may get the disease, but none of their daughters will, even though they may be carriers. The patient himself, being an affected male, will never have any children with the disease.

His daughters may be carriers, perhaps, but their eyes will be normal just the same. Of course, it is vitally important for the patient to know the odds of having affected children; whereas, it is only of academic or eugenic importance for him to appreciate the far-reaching problems of normal children who may be carriers. The important thing for him to realize is that his children will never have the disease.

If the patient has a brother whose eyes are normal, this brother will not transmit the disease. In contrast, the normal sisters and normal daughters will likely give it to 50 percent of their sons.

Figure 3 is the family tree of a 22-year-old patient with choroideremia, a sex-linked trait. It is evident that only males are affected and the disease was contracted via the asymptomatic carrier mother. However, as happens to be the case with choroideremia, this mother had fine pigment dots in her optic fundi even though her vision and fields were normal. In this way, it was possible to identify the seemingly normal mother as one who might transmit choroideremia.

### COMMENTS

The ocular diseases discussed so far are usually inherited in only one way; thus, glaucoma and cataracts are practically always inherited as dominant traits and very rarely demonstrate recessive or sex-linked characteristics. Once the malady has been diagnosed, one can make predictions and advise the patient, even if there is no detailed

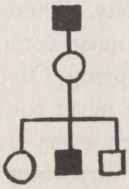

Fig. 3 (Manchester). Sex-linked recessive choroideremia.

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* There are no significant eye diseases inherited specifically as sex-linked affecting women.

family tree. There is another group of important diseases which may be transmitted by either of these three methods either dominant, recessive or sex-linked recessive. For these, two or three generations must be plotted before one can decide which type of inheritance he is dealing with.

Laymen often ask about the heredity of refractive errors, color blindness, and eye color. Obviously these are academic questions, but still their frequent repetition stimulates the search for a ready answer. Consistently accurate predictions cannot be made about refractive errors. Because ametropia depends upon the corneal curvature, anterior chamber depth, and refractive index of the lens as well as the axial length of the eye, it is impossible to fathom the mechanisms involved in this kind of inheritance. In general, the small refractive errors show dominant characteristics, and the larger refractive errors show recessive characteristics. The common forms of color blindness (Daltonism) have a sex-linked recessive pattern. There are three pairs of genes controlling eye color and, therefore, this condition is unpredictable although, in general, brown is dominant over blue.

One vital omission may be apparent by this time. No consideration has been given to those situations in which a mating occurs between a man and a woman, both of whom are affected by the same ocular disease. For example, consider a marriage between a man who has survived after treatment for retinoblastoma and a woman who has likewise been treated for retinoblastoma, or the case of a man and wife who are both nearly blind from pigmentary degeneration of the retina. Such unhappy circumstances are possible but extremely unlikely. These would be rare situations with most complicated possibilities for any offspring. Of course, most ophthalmologists are never confronted with such a problem in their every-day practice.

A list of the important eye diseases has been compiled and classified (table 3). There are exceptions to the classification of course. Nearly all of them, including cataract, glaucoma, and macular dystrophy, may appear sporadically without any hereditary features. Thus it would be ridiculous to advise any glaucoma patient that his descendents are likely to transmit this trait unless there is evidence that preceding generations have been affected.

TABLE 3

CLASSIFICATION OF THE IMPORTANT HEREDITARY EYE DISEASES

- DOMINANT
  - Concomitant strabismus
  - Duane's syndrome
  - Ptosis with epicanthus
  - Phakomatoses
  - Blue sclerotic syndrome
  - Cataracts (congenital and postnatal)
  - Retinoblastoma
  - Glaucoma
  - Dacryocystitis
  - Arachnodactyly
  - Corneal dystrophy of granular type and lattice type
  - Aniridia
  - Recurrent corneal erosion
  - Heterochromia congenita
  - Dominant optic atrophy of children
- RECESSIVE
  - Pure albinism
  - Microphakia
  - Amaurotic family idiocy
  - Laurence-Moon-Biedl syndrome
  - Hydrophthalmos
  - Corneal dystrophy—macular type
- SEX-LINKED
  - Choroideremia
  - Red-green colorblindness
  - Megalocornea
  - Lebers' hereditary optic atrophy*
- DISEASES WITH UNPREDICTABLE MODES OF INHERITANCE
  - Cerebromacular degeneration
  - Macular dystrophy
  - Congenital absence of rods
  - Congenital absence of cones
  - Keratoconus—usually alternating with high astigmatism
  - Craniofacial anomalies
  - Hereditary ataxias
  - Elastosis dystrophica—Groenblad-Strandberg syndrome—pseudoxanthoma elasticum
  - Nystagmus
  - Pigmentary degeneration of retina
  - Progressive external ophthalmoplegia
  - Gyrate atrophy
  - Fuchs' epithelial-endothelial dystrophy

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* This should be considered sex-linked recessive in advising patients, although there are rare instances of affected females. Another unusual feature is the fact that for some reason affected males do not transmit to any future generations.

Table 2 considers facts which may be given the patient and his relatives in answer to their question of how likely are their children to develop the disease. No consideration whatever has been given to the problem of how many unaffected children may be carriers. This is a matter of eugenic importance and, being outside the scope of ophthalmology, is best left to the opinion of specialists in that field.

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